Magnetoencephalography (MEG) and Diffusion Tensor Imaging (DTI) for Differential Diagnosis in Mild TBI and PTSD

Presented by Mingxiong Huang (PhD): Integrated Research from VASDHS, UCSD, and NMCSD

NAVY AND MARINE CORPS COMBAT & OPERATIONAL STRESS CONFERENCE 2010:
"TAKING ACTION, MEASURING RESULTS"

NAVAL CENTER
COSC
COMBAT & OPERATIONAL STRESS CONTROL

Acknowledgements

NAVAL CENTER COSC
COMBAT & OPERATIONAL STRESS CONTROL

UCSD

VASDHS

Dewleen Baker, M.D.
Roland Lee, M.D.
Sharon Nichols, Ph.D.
Rebecca Theilmann, Ph.D.
Michael Levy, M.D.
Raul Coimbra, M.D.
John D'Andrea, M.D.
Doris Trauner, M.D.
Tao Song, Ph.D.
Annemarie Angeles
Ashley Robb

Angela Drake, Ph.D.
Robert McLay, M.D.
Paul Hammer, M.D.
Martin Holland, M.D.
Sarah Asmussen, Ph.D.
Catherine Cheung

M.X. Huang, Ph.D.,

Headline

- The lack of positive findings in mild TBI (mTBI) and PTSD using conventional neuroimaging techniques.
- New neuroimaging techniques: magnetoencephalography (MEG) and diffusion tensor imaging (DTI)
- MEG and DTI for mTBI
- MEG for PTSD
- Differential diagnosis of mTBI and PTSD

NAVAL CENTER COSC COMBAT & OPERATIONAL STRESS CONTROL

The lack of positive findings in mild TBI and PTSD using conventional neuroimaging techniques

- PTSD and Traumatic brain injury are leading cause of sustained physical, neurological, cognitive, and behavioral deficits in military personnel and civilian population.

- Differential diagnosis of mild TBI (mTBI) and PTSD is crucial since they require different treatments, but can be challenging due to symptom-overlap.

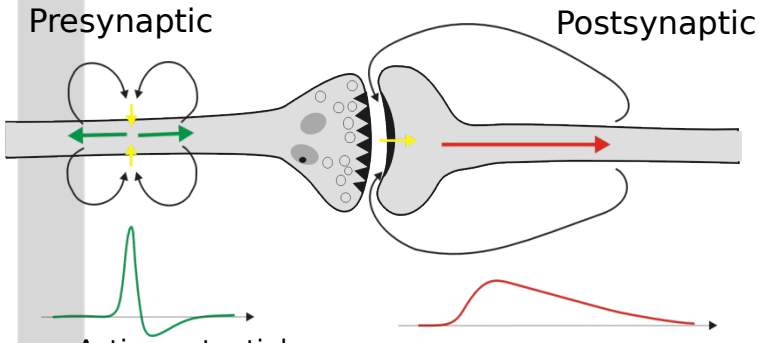
- Conventional CT and MRI focus on blood products with limited sensitivity for diagnosing mTBI and PTSD: Among civilian mTBI patients with Glasgow Coma Scales of 13, 14, and 15, only 28%, 16%, and 4% showed visible intracranial lesions with conventional CT or MRI , respectively. Conventional MRI and CT do not detect abnormality in PTSD either.

- More sensitive neuroimaging techniques, such as MEG and DTI are needed to detect subtle neuronal injuries due to mTBI and PTSD

Headline

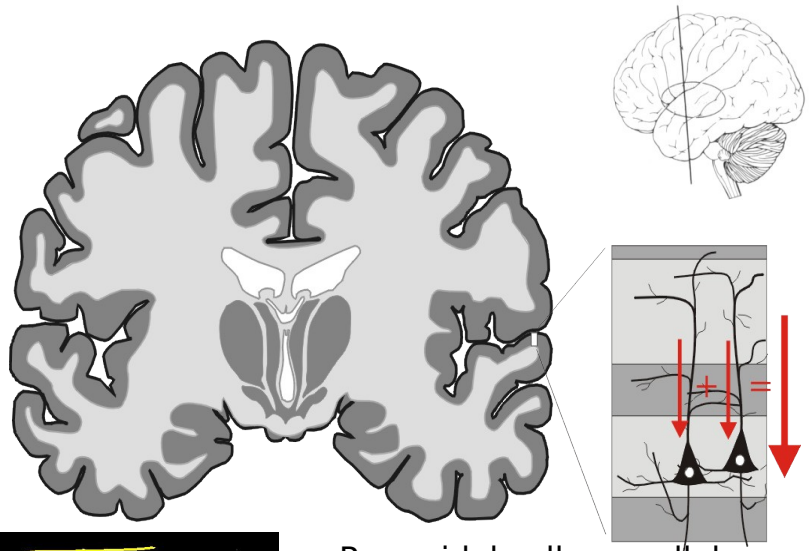
- The lack of positive findings in mild TBI (mTBI) and PTSD using conventional neuroimaging techniques.
- New neuroimaging techniques: magnetoencephalography (MEG) and diffusion tensor imaging (DTI)
- MEG and DTI for mTBI
- MEG for PTSD
- Differential diagnosis of mTBI and PTSD

Neuronal currents in axons and dendrites

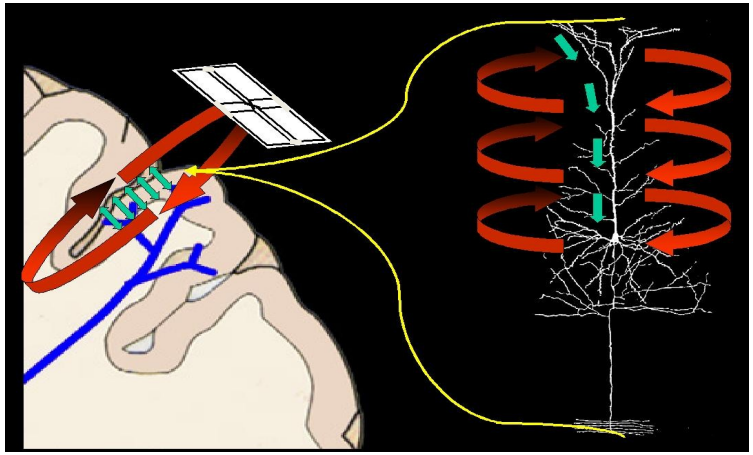


- Action potentials:
  - Fast: no/little temporal summation
  - Cancellation: fields diminish rapidly

Parallel dendrites

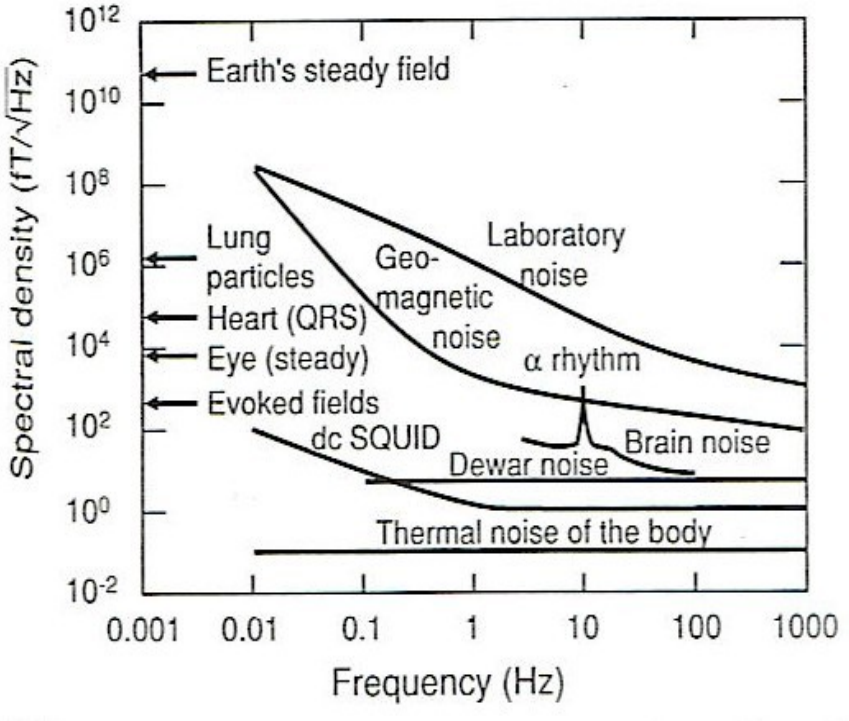


Pyramidal cells: parallel orientation => spatial summation



Non-invasive MEG Technique with 1 ms Temporal Rresolution and several mm Spatial Resolution in Cortex

MEG signal is weak

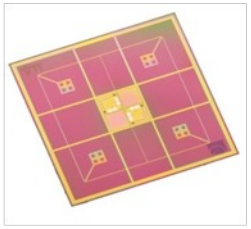


Multiple Layer Magnetic Shielded Room at the UCSD

Shielding factors:
0.01Hz: 65dB
0.1 Hz: 73dB
1 Hz: 108dB
10Hz: 160dB

Whole-Head Elekta-Neuromag MEG System with 306 channels and GE 1.5T MRI System

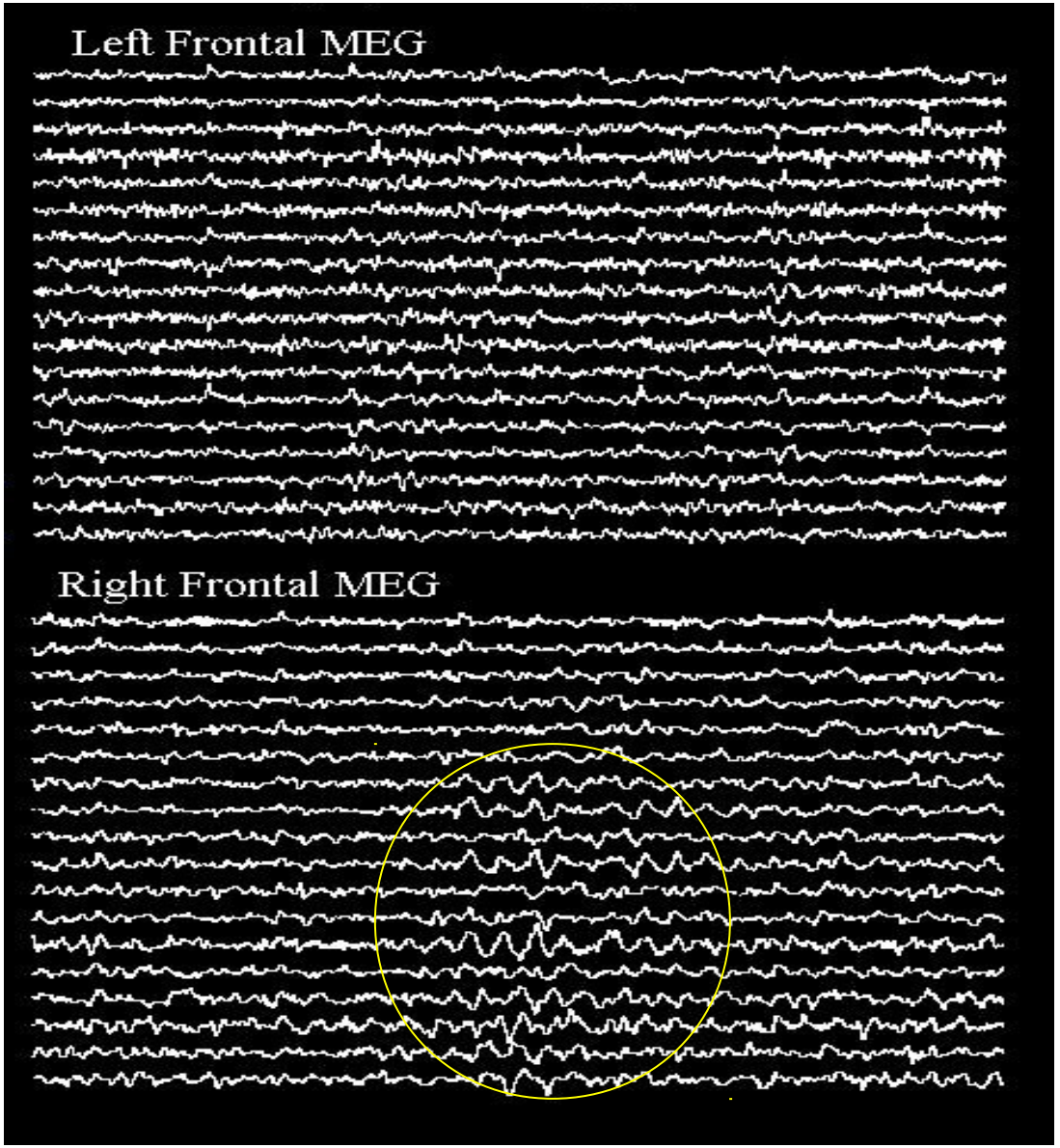
MEG SQUID Sensor Array



MRI field strength: 1.5 T
MEG SQUID sensitivity: ~ fT (10^{-15} T)

Abnormal MEG Slow-waves are Characteristics of Neurological Injuries in the Brain

- Stroke
- Brain tumor
- Epilepsy
- Traumatic brain injury



M.X. Huang, Ph.D., mxhuang@ucsd.edu

Using MEG and DTI to detect subtle injury in mTBI patients

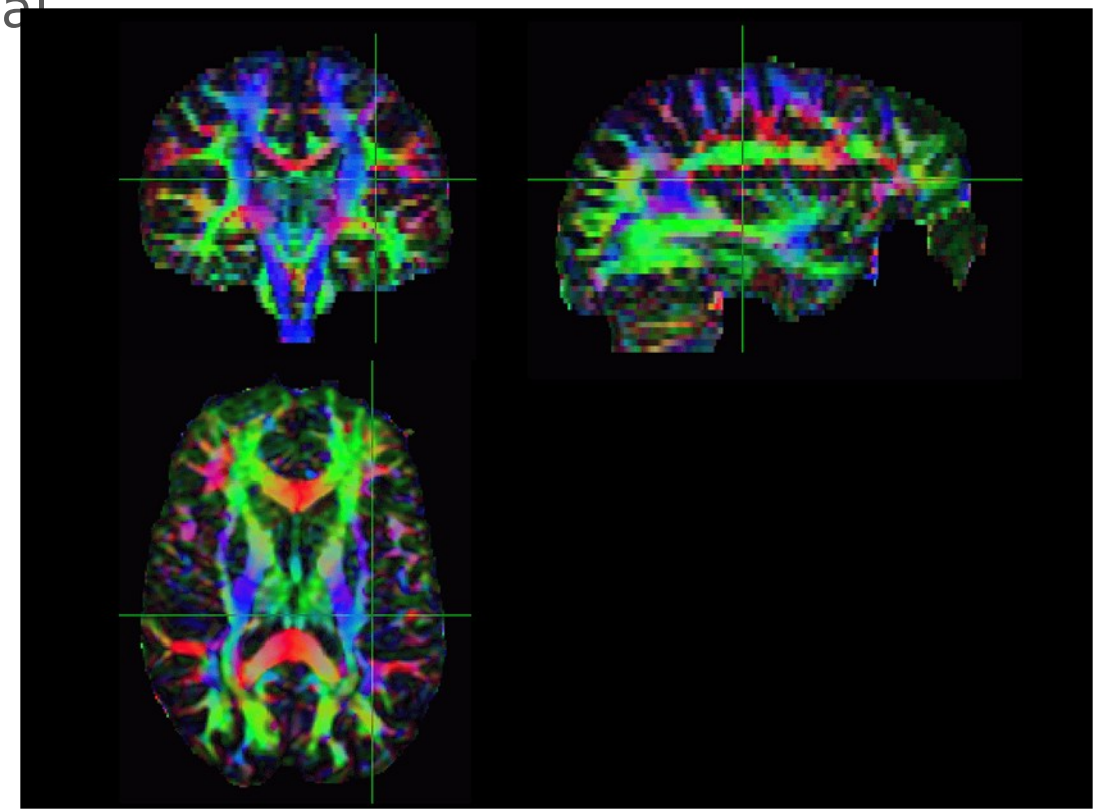
- Injured brain tissues in mTBI patients generate abnormal low-frequency neuronal magnetic signal that can be measured and localized by MEG [1],
- The cause of the MEG slow-waves in TBI patients is not fully understood. This issue limits the application of MEG slow-wave detection in the clinical diagnosis of mTBI.
- Invasive Electro-neurophysiological studies on cats showed that polymorphic slow waves (delta frequency 1-4 Hz) can be produced in gray-matter by lesions in the white matter. It was concluded that slow-wave generation was the result of de-afferentation to the cortex [2][3].
- We hypothesize that abnormal slow-waves in mTBI patients originate from cortical gray-matter areas which have experienced de-afferentation due to axonal injuries in white-matter fibers, similar to findings in animal studies in cats.
- We need converging imaging evidence of axonal injury in white-matter fibers that link to gray-matter areas that generate MEG slow-waves in mTBI patients. We hypothesize that DTI provide crucial evidence in confirming our assumption.
- White-matter tracts injured by mTBI show reduced anisotropy in DTI.

Diffusion Tensor Imaging (DTI)

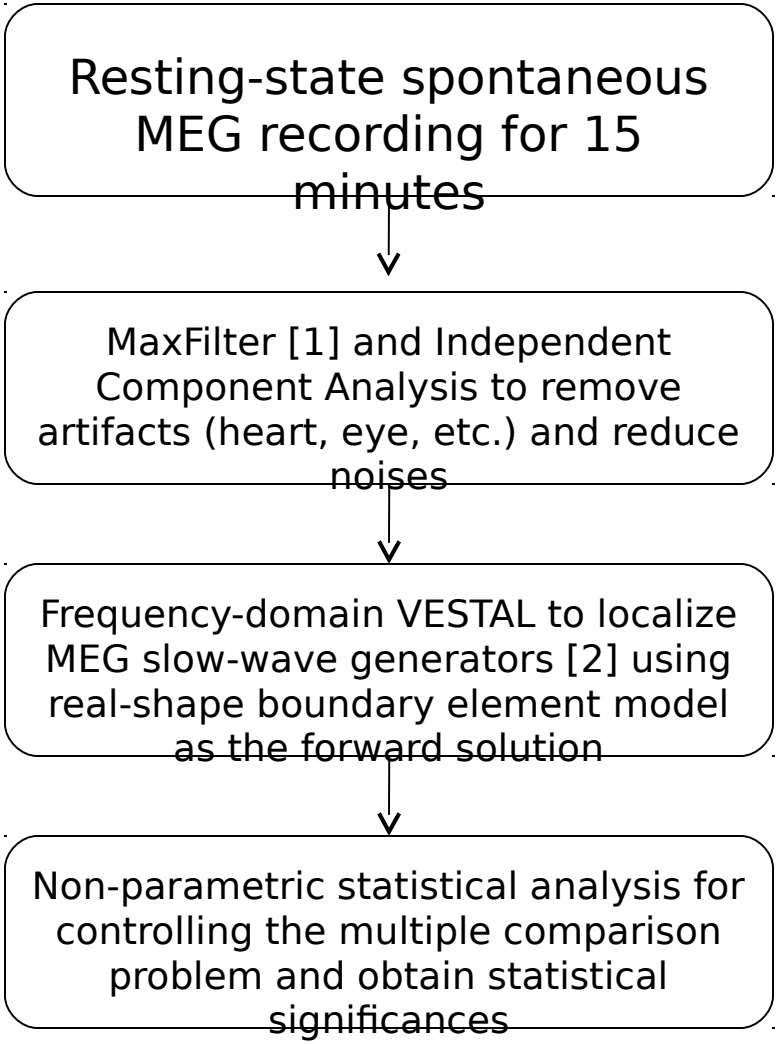
- DTI is an advanced MR imaging technique based on the Brownian motion of water through tissues
- It measures how easy that water molecules move along the direction of white matter fibers versus the directions perpendicular to the fibers.
- TBI causes tissue shearing in the white matter fibers that leads to reduction of DTI signal

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

$$FA = \frac{\sqrt{3\left[(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2\right]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

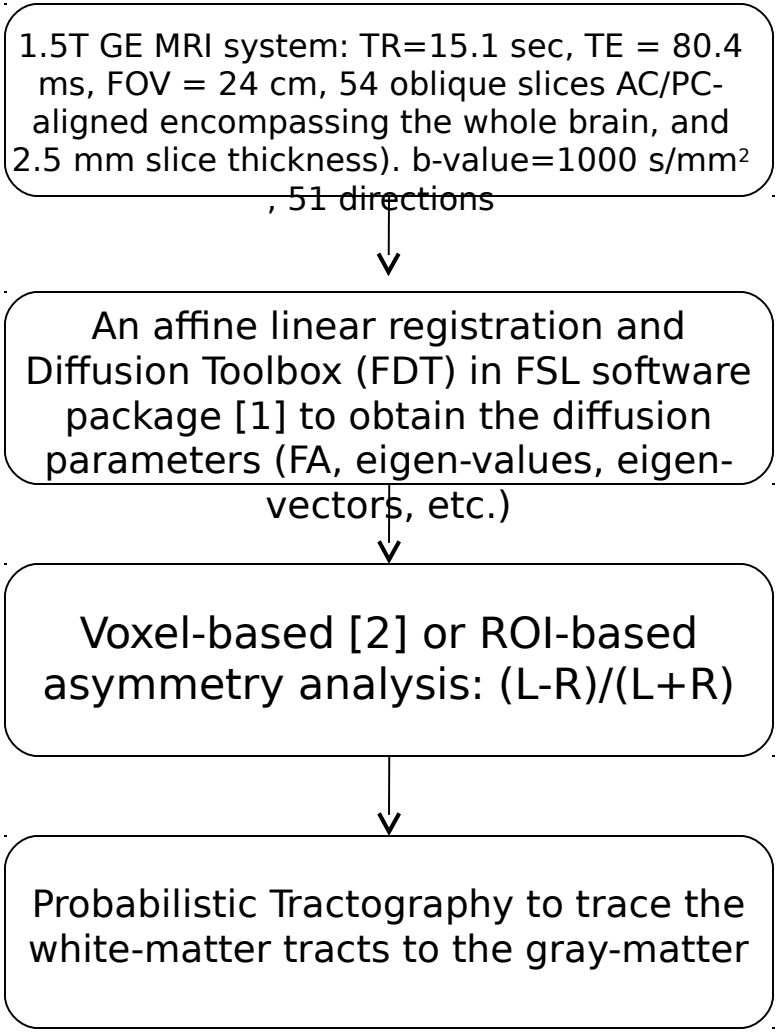


MEG Data Acquisition and Analysis for Detecting Abnormal Slow-waves


Resting-state spontaneous MEG recording for 15 minutes
MaxFilter [1] and Independent Component Analysis to remove artifacts (heart, eye, etc.) and reduce noises
Frequency-domain VESTAL to localize MEG slow-wave generators [2] using real-shape boundary element model as the forward solution
Non-parametric statistical analysis for controlling the multiple comparison problem and obtain statistical significances

[1] Taulu S and Simola. Phys. Med. Biol. 51: 1759-1768, 2006.
[2] Huang, et al., NeuroImage 31(3):1025-1037, 2006.

DTI Data Acquisition and Analysis


1.5T GE MRI system: TR=15.1 sec, TE = 80.4 ms, FOV = 24 cm, 54 oblique slices AC/PC-aligned encompassing the whole brain, and 2.5 mm slice thickness). b-value=1000 s/mm^2 , 51 directions
An affine linear registration and Diffusion Toolbox (FDT) in FSL software package [1] to obtain the diffusion parameters (FA, eigen-values, eigen-vectors, etc.)
Voxel-based [2] or ROI-based asymmetry analysis: (L-R)/(L+R)
Probabilistic Tractography to trace the white-matter tracts to the gray-matter

Conventional Clinical MRI
- T1-weighted
- T2*-weighted
- T2-weighted with ASSET
- FLAIR
- DWI

[1] Behrens et al., Magn Reson.Med. 50: 1077-1088, 2003 -- fsl.fmrib.ox.ac.uk/fsl/fdt/
[2] Smith et al., Neuroimage 31: 1487-1505, 2006.

Headline

- The lack of positive findings in mild TBI (mTBI) and PTSD using conventional neuroimaging techniques.
- New neuroimaging techniques: magnetoencephalography (MEG) and diffusion tensor imaging (DTI)
- MEG and DTI for mTBI
- MEG for PTSD
- Differential diagnosis of mTBI and PTSD

NAVAL CENTER
OSC
ERATIONAL STRESS CONTROL

The San Diego
Union-Tribune.

Friday
May 9, 2008

50¢
Final

Mexican national police chief gunned down

Edgar Eusebio Millán Gómez, public face of war on drugs.

Killing a setback to anti-drug effort

By Manuel Roig-Franzia
THE WASHINGTON POST

MEXICO CITY — Gunmen assassinated Mexico's national police chief yesterday, blasting him with nine bullets outside his home in the capital and dealing a significant setback to the government's campaign against drug cartels.

Edgar Eusebio Millán Gómez, the public face of Mexico's offensive against drug cartels, became the highest-ranking law enforcement official to be killed since the launch of the effort 17 months ago.

Alejandro Gertz Manero, Mexico's former public safety minister, said yesterday on Radio Formula that Millán's killing demonstrated "a desire to generate an atmosphere of terror."

Mexico's drug-and-violence problem engulfs the entire country, swamping cities along the U.S.-Mexico border and rugged drug-cartel redoubts in the western mountains, and piercing into the heart of national power in Mexico City. The capital has been the scene of four assassinations of high-ranking federal police officials in roughly a week.

Millán had ordered thousands of federal police to take over crime-fighting responsibilities from local police suspected of aiding drug traffickers. Those field operations — often conducted with the military — have led to widespread resentment among local and state law

SEE Police chief, A12

Navy hospitals, Camp Pendleton, UCSD join battle against brain injuries

Researchers Mingxiong Huang (left) and Roland Lee look over brain scans at their brain imaging lab at UCSD. They are working on a pilot program sponsored by the Navy and the Department of Veterans Affairs. *Bruce K. Huff / Union-Tribune*

Head trauma getting attention

By Rick Rogers
STAFF WRITER

Military officials are rolling out programs in the county and nationwide to take on traumatic brain injuries, a signature casualty of the Iraq and Afghanistan wars.

The projects are aimed at keeping hundreds of thousands of troops with brain trauma, including roughly 720 a year at Camp Pendleton, from slipping through the cracks. They reflect the armed forces' growing recognition of a condition long overshadowed by another mental health affliction — post traumatic stress disorder.

Combat zones are filled with ways to cause a traumatic brain injury, commonly known as TBI. A roadside bomb throws a Marine's head against his Humvee or shrapnel pierces a soldier's skull and damages brain tissue.

About one in every five troops who have served in Iraq or Afghanistan have experienced a TBI, according to a major study released last month by the Rand Corp. Nearly half of the military personnel have not sought diagnosis or treatment, the report said.

Angela Drake, director of Camp Pendleton's Defense and Veterans Brain Injury Center, tested a lance corporal by timing his ability to place keys in a pegboard. *Eduardo Contreras / Union-Tribune*

Any day now, Camp Pendleton is expected to officially open the Navy Medicine West Office of Neurotrauma on the base.

SEE Brain injuries, A8

TRAUMATIC BRAIN INJURY

Names: Also called acquired brain injury.

Causes: Occurs when sudden trauma damages the brain, such as when the head violently hits an object or when something pierces the skull and enters brain tissue.

Mild cases: Person remains conscious or loses consciousness for a few seconds or minutes. Other symptoms include temporary headache, confusion, dizziness, blurred vision, ringing in the ears, bad taste in the mouth, fatigue, a change in sleep patterns, mood swings and trouble with memory, concentration or thinking.

Moderate and severe cases: Many of the symptoms for mild cases, plus persistent or worsening headache, repeated vomiting or nausea, convulsions or seizures, dilation of one or both eye pupils, slurred speech, loss of coordination and weakness or numbness in the extremities.

SOURCE: National Institute of Neurological Disorders and Stroke

Personal concierge services buy clients precious time

Local businesses help manage hectic lifestyles

By Jane Clifford
FAMILY EDITOR

John Frager is a busy guy. He's a husband, a father and a real-estate executive. When his dad got sick, he worried about his mom adding caregiver to everything else she was doing, and his own schedule left little time to help. But he did have an idea.

"I gave my parents some time as a gift," the Carmel Valley resident recalls.

That time was in the form of services from Lisa Barnett, founder of Your Personal Concierge, a lifestyle management company that serves clients primarily in North County.

"We wanted to help, but it's almost like they felt guilty calling us all the time," said Frager, the chief executive officer of Grubb & Ellis Commercial/BRE. "Both were in their 70s, and it was a pretty hectic period for all of us. She was helpful in getting some things done for us."

The idea of time-pressed families hiring someone to take care of things for them is growing in popularity. Barnett's company, in business since 2003, is one of several in the county helping to ease the stress of working parents, overburdened couples and single professionals.

For a fee, they drop off or pick up dry cleaning, shop for groceries, take the car in for service, research home repairs,

SEE Errands, A12

Lisa Barnett, founder of Your Personal Concierge, ran a wine-buying errand for a client. *Cristy Pascual / Union-Tribune*

House approves mortgage rescue bill

Bush has threatened veto but may be open to talks

By Lori Montgomery
THE WASHINGTON POST

WASHINGTON — The House approved an ambitious plan yesterday to rescue hundreds of thousands of homeowners at risk of foreclosure by helping them trade exotic loans with rapidly rising monthly payments for more affordable mortgages backed by the federal government.

Backing a White House veto threat, 39 Republicans joined Democrats in supporting the bill, the centerpiece of a broader housing package that represents Washington's most aggressive response to the nation's housing crisis. The measure aims to unfreeze mortgage markets by expanding the Federal Housing Administration's reach and strengthening mortgage giants Fannie Mae and Freddie Mac. It also would create a $7,500 tax credit for first-time home buyers to try to boost sales and slow plummeting home prices.

GOP House leaders blasted the bill as a bailout for speculators and irresponsible borrowers. But the measure, sponsored by House Financial Services Committee Chairman Barney Frank, D-Mass., gained strong support from rank-and-file Republicans worried that escalating foreclosures are ruining lives and decimating neighborhoods.

Despite President Bush's condemnation of the bill earlier this week, White House officials also seemed to leave the door open to negotiation. In the Senate, key Republicans are working with Demo-

SEE Housing, A10

As problems beset church, worshippers left in droves

Congregation struggling with foreclosure, rumors

By Sandi Dolbee
STAFF WRITER

It's Sunday morning at Ambassador Family Church and despite the upbeat music and smiling greeters, there are signs that all is not well.

Monitors and speakers play eerily to empty rows of upholstered chairs. The 200 or so people gathered for worship are swallowed up in an auditorium built for a larger crowd.

Ron Satrape

Barry Cook, the 44-year-old founder of this once-thriving, multiethnic church, is absent. He welcomes people in a videotaped message.

Ron Satrape, a preacher and church consultant from New England, tells the congregation that their pastor is taking time off to "insulate" himself. "I want you to know that God is at work and we are on the rebound."

What goes unspoken is how much there is to rebound from.

An estimated 600 members have left Ambassador Family Church in Oceanside. Unable to pay its mortgage, the church has been foreclosed upon, an action rare enough that observers can't remember the last time it happened to a local congregation.

But the rise and fall of this charismatic, nondenominational congregation is about more than financial default.

It's also a cautionary tale of what can happen when an autonomous church is

SEE Church, A12

A COPLEY NEWSPAPER
7 sections
66 pages

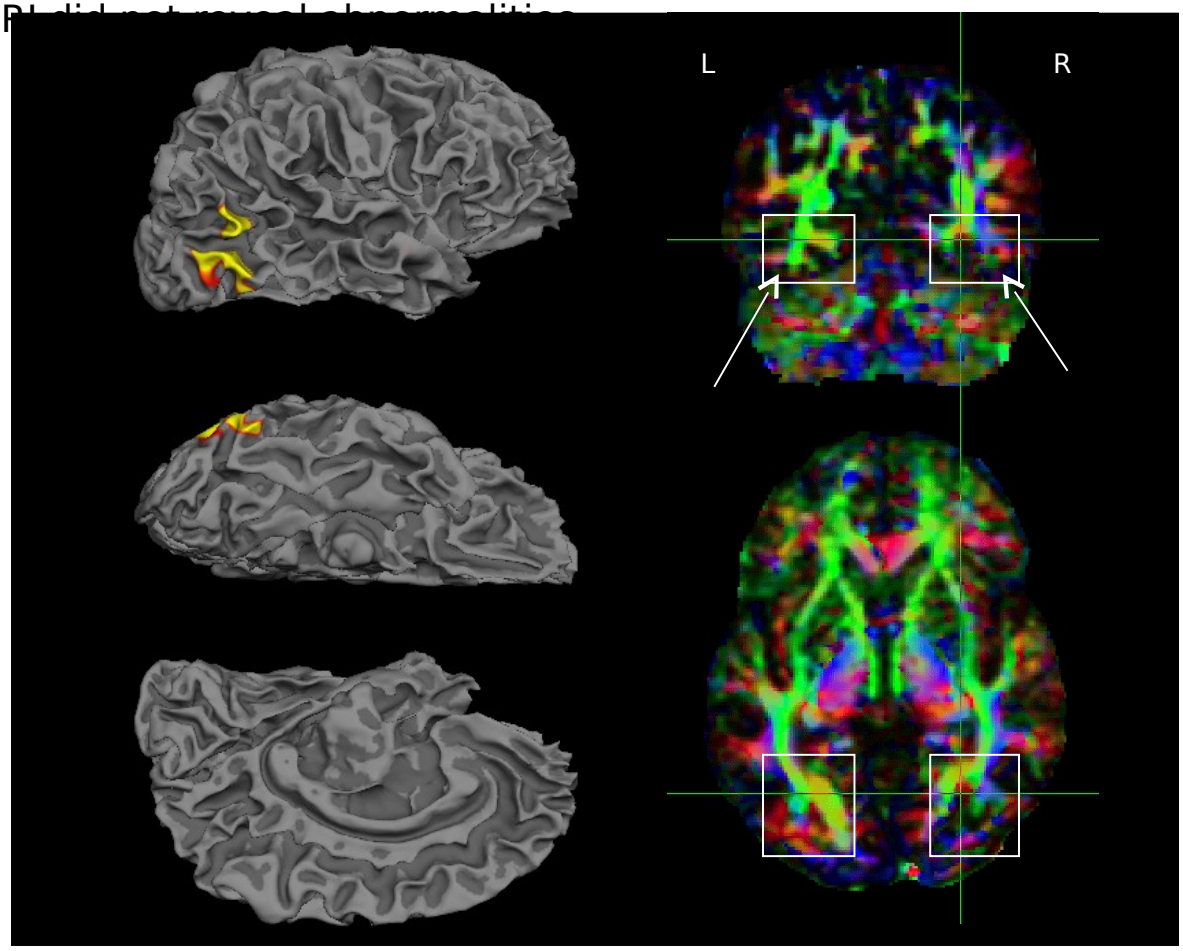
Bridge F3 | Crossword F2 | Horoscope F4 | Obituaries B5
Classifieds F1 | Dear Abby E11 | Lottery A2 | Television E9
Comics E10 | Editorials B8 | Movers E4 | Weather C4

U-T VOICE | MICHAEL STETZ, JENNIFER DAVIES
Husband and wife critics weigh in on the date movie "What Happens in Vegas." Currents, E1

FOR BREAKING NEWS ONLINE, GO TO: uniontrib.com

Mild Blast-induced TBI with NO Visible Lesion on MRI, but with Abnormal MEG Slow-waves and DTI

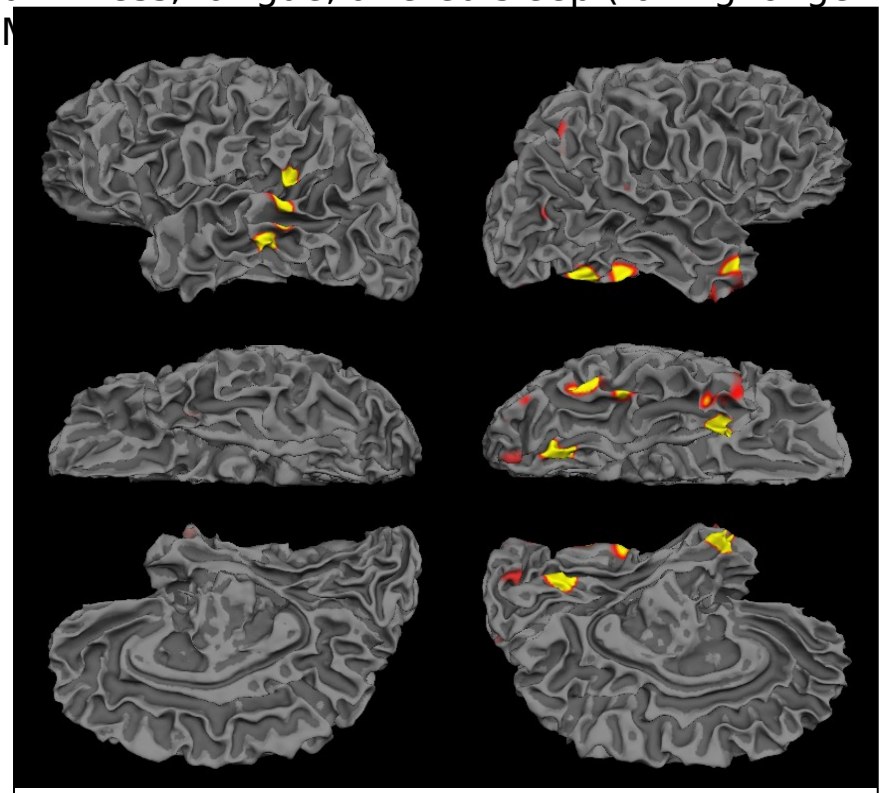
History: 43-year-old male soldier who suffered blast-induced mild TBI due to anti-tank mine. He lost consciousness for less than 1 minute. Following the incident, he experienced persistently the following symptoms: dizziness, fatigue, irritability, affective speech, memory loss, changes in social personality, balance problem, and headaches. MRI did not reveal abnormalities.



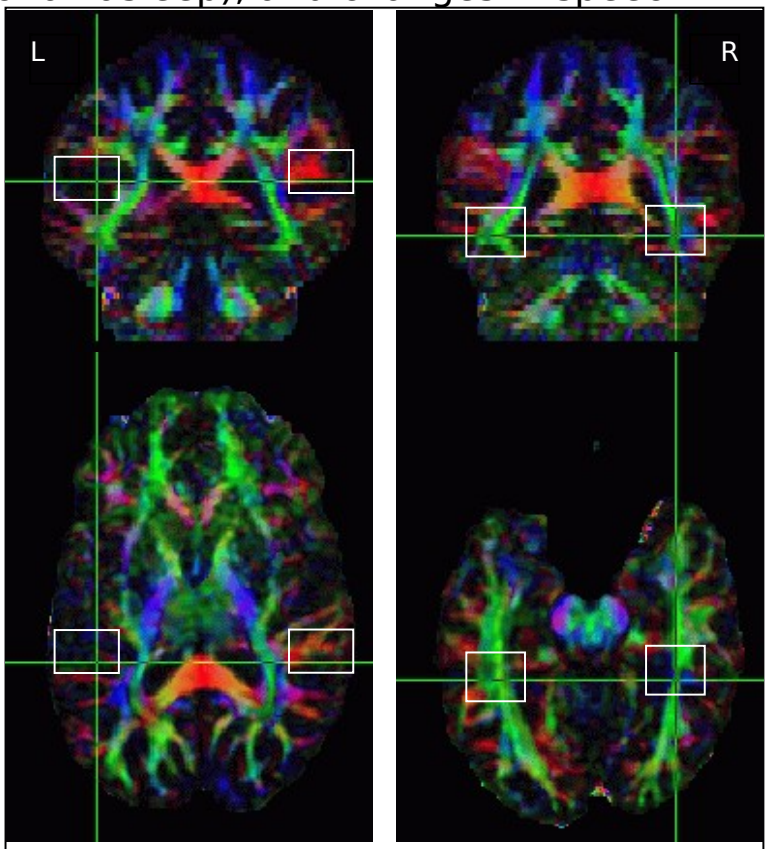
Right temporal-occipital junction exhibits both abnormal MEG slow-waves as well as reduced DTI signal

Mild TBI due to Several Sport-related Accidents with NO Visible Lesion on CT or MRI, but with Abnormal MEG Slow-waves and DTI

- History: 17-year old, male football player, who suffered 3 mTBIs while playing football. 1st and 2nd concussions separated by a few weeks, and 3rd a few months later. After the 1st injury: headaches. After the 2nd injury: headaches, dizziness, and extreme fatigue while performing any mental task. Following the 3rd concussion: pressure headaches, dizziness, fatigue, altered sleep (taking longer to fall asleep), and changes in speech.



MEG results show abnormal slow-waves generated from two regions in a TBI patient: 1) left column -- left lateral superior-posterior temporal region, 2) right column --- right inferior-temporal areas. Color threshold p<0.01. The top, middle, and bottom rows are lateral-view, ventral-view, and middle-view, respectively.

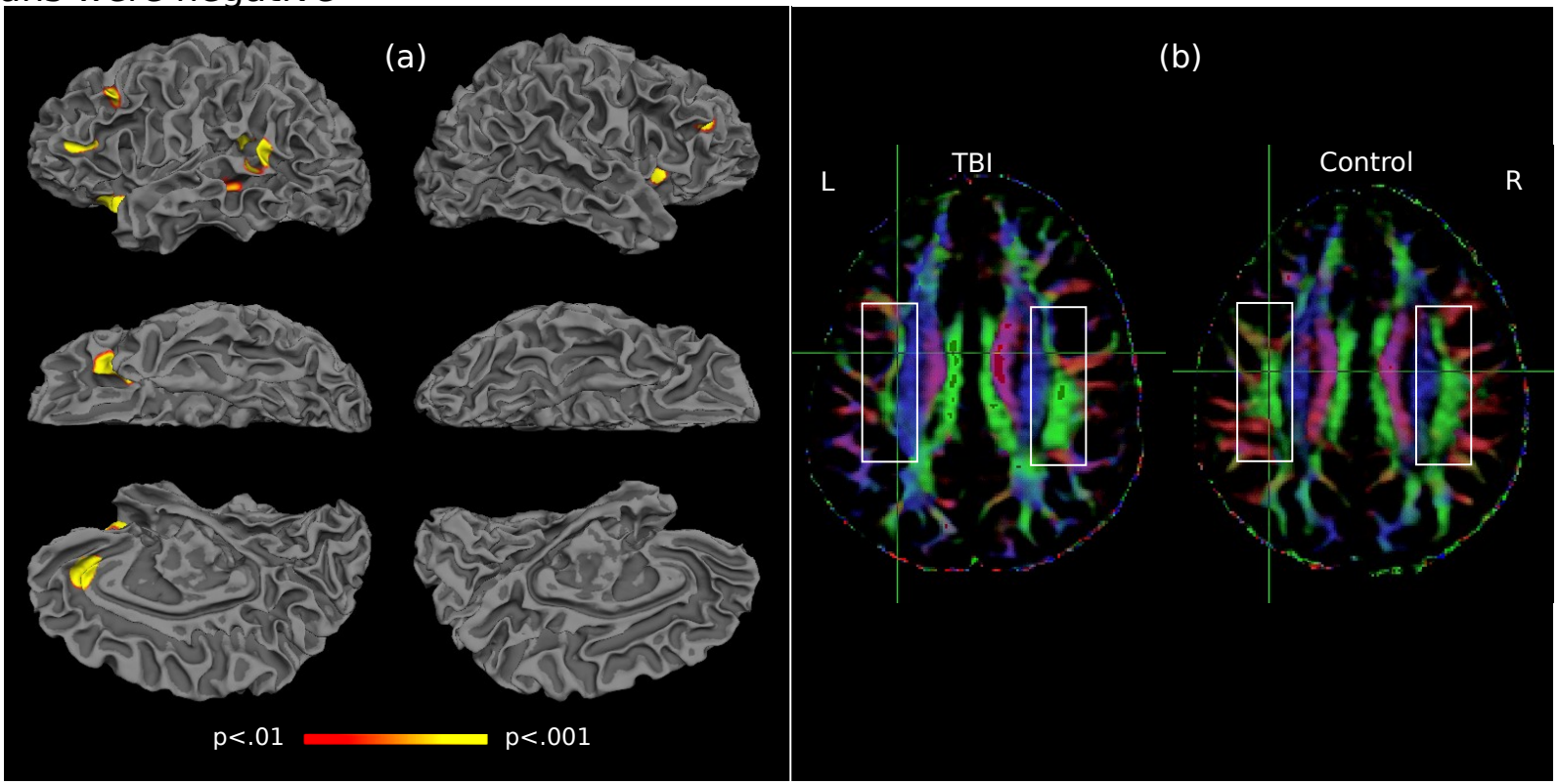


Left column: coronal and axial view show abnormal DTI in superior-posterior temporal lobe of the left hemisphere in a TBI patient. Right column: abnormal DTI in inferior-temporal lobe as part of the inferior longitudinal fasciculus of the right

Huang et al., J. NeuroTrauma 2009; 26: 1213-

Mild TBI patient with blast injury with NO Visible Lesion on CT or MRI, but abnormal MEG slow-waves and DTI findings in a Major white-matter tract

History: blast-induced mTBI patient (male, age 27) caused by an IED. He experienced a loss of consciousness for several seconds and he experienced post-concussive symptoms of fatigue, disordered sleep, dizziness, irritability, anxiety, psychosocial and personality disturbances, and memory loss since the incident. His clinical MRI and CT scans were negative



Multiple neuronal sources that generated MEG slow-waves in a mild TBI patient. Bilateral LPFC, left OFC, left ACC, and left temporal areas regions showed abnormal slow-wave activities. DTI reveals profound abnormality of left SLF in a TBI patient. The normal control showed much thicker anterior-posterior oriented diffusion in SLF (green color) than the TBI patient in the left hemisphere. The white boxes are used for ROI analysis.

Huang et al., J. NeuroTrauma 2009; 26: 1213-1226.

Regions that generated MEG delta-waves and showed DTI abnormalities in mTBI with "normal" CT/MRI (partial list)

	Cause of TBI	MEG slow-wave foci	Foci with DTI abnormalities
Case 1, Male, Age 43	Blast	R posterior-temporal & anterior-occipital lobe	R posterior-temporal & anterior-occipital lobe
Case 2, Male, Age 17	Sport (Football), three incidents	L posterior superior temporal lobe; R inferior temporal-occipital regions (3 areas)	L posterior superior temporal lobe; R inferior longitudinal fasciculus
Case 3, Male, Age 14	Sport (Hockey), hit to R temporal	R inferior temporal–occipital lobe	R inferior longitudinal fasciculus in temporal lobe.
Case 4, Male, Age 27	Blast	L lateral prefrontal lobe; L temporal-parietal junction; L orbital frontal lobe; L anterior cingulate; R lateral prefrontal lobe	L Superior longitudinal fasciculus
Case 5, Female, Age 12	Sport (Soccer), fall on back of the head	L and R occipital lobes; L posterior temporal lobe	L-R asymmetry in optical tracts in the occipital lobes; L posterior temporal lobe
Case 6, Male, Age 16	Sport (Football)	R inferior parietal lobe	Within normal range
Case 7, Male, Age 21	Motor Vehicle Accident	R lateral prefrontal cortex; R central sulcus; R inferior posterior parietal area; R ventral temporal area	DTI findings within normal range, but PET shows abnormal metabolic signals in: R lateral prefrontal cortex; R parietal lobe; R temporal lobe; R occipital lobe

Huang et al., J. NeuroTrauma 2009; 26: 1213-1226.

Summary of MEG and DTI findings for mTBI

- The multimodal imaging approach with MEG and DTI is substantially more sensitive than conventional CT and MRI in detecting subtle neuronal injury in mTBI.
- MEG slow-waves accrue from de-afferentation in cortical gray-matter neurons that connect to white-matter fibers with axonal injury.
- MEG slow-waves in TBI patients can show a focal, multi-focal, and/or diffuse pattern with multiple generators, indicating more diffuse cortical de-afferentation due to axonal injury.
- Reduced anisotropy in local white-matter fiber tracts (as measured by DTI) will lead to focal abnormal delta-waves (as measured by MEG) from cortical gray-matter overlaid with these local tracts. On the other hand, reduced anisotropy in major white-matter fiber tracts will lead to multi-focal or distributed patterns of abnormal delta-waves generated from multiple cortical gray-matter areas that can be remote in location but functionally and structurally linked by the injured major white-matter fibers.
- In some cases, abnormal MEG delta-waves were observed in mild TBI patients without DTI abnormality, indicating that MEG

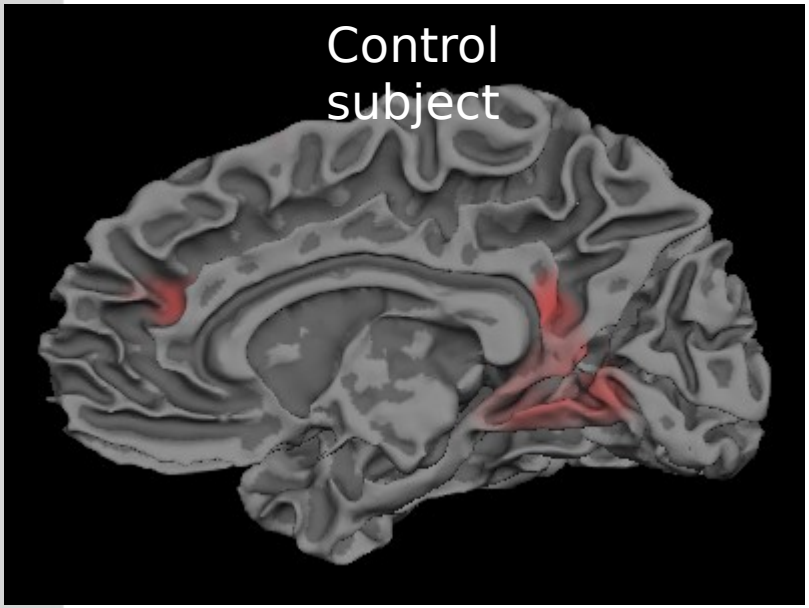
Headline

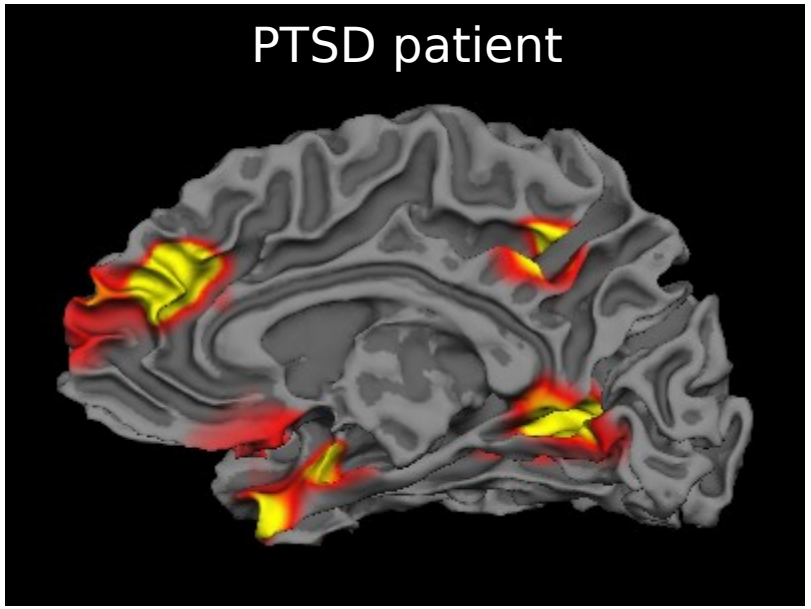
- The lack of positive findings in mild TBI (mTBI) and PTSD using conventional neuroimaging techniques.
- New neuroimaging techniques: magnetoencephalography (MEG) and diffusion tensor imaging (DTI)
- MEG and DTI for mTBI
- MEG for PTSD
- Differential diagnosis of mTBI and PTSD

Problems with conventional neuroimaging techniques for diagnosing PTSD

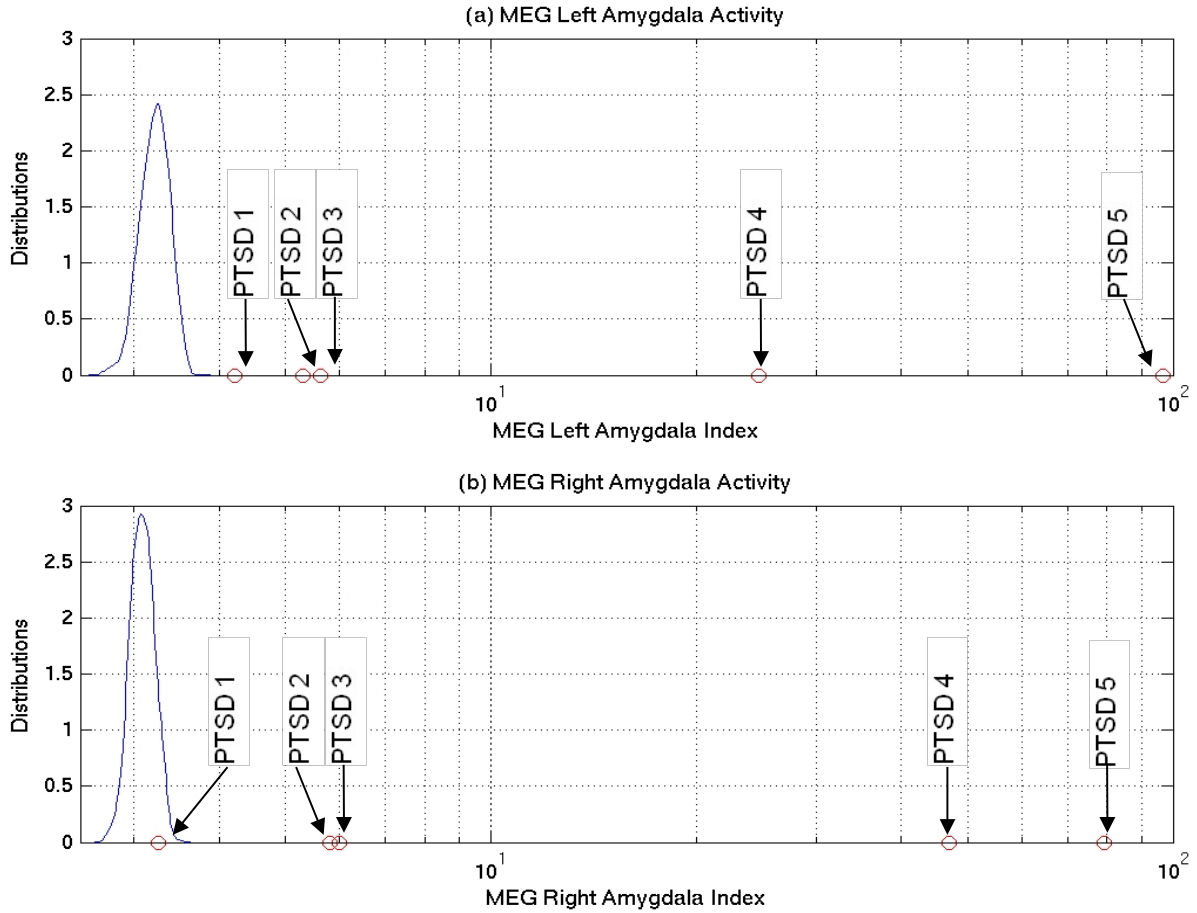
- Conventional structural imaging exams (MRI and CT) are usually negative for PTSD.
- Group-based SPECT, PET, and fMRI studies revealed increased/altered blood flow patterns suggesting increased responsivity in pre-frontal cortex (PFC), anterior cingulate cortex (ACC), amygdala, and insula regions in PTSD, compared with healthy controls.
- Despite important progresses, it is difficult for the above group-based functional imaging techniques to diagnose PTSD in specific individuals

MEG resting-state exam reveal hyper-activated network in PTSD





MEG resting-state exam reveal hyper-activated amygdala in PTSD



Differential diagnosis of mTBI and PTSD using MEG and DTI

- Patients mTBI *without* PTSD show: abnormal MEG slow-waves, abnormal DTI.
- Patients with PTSD *without* mTBI show: hyper-activated ACC, amygdala, and hippocampus network.
- Patients with both mTBI and PTSD show: abnormal MEG slow-waves, abnormal DTI, and hyper-activated network including ACC, amygdala, and hippocampus.

NAVAL CENTER COSC
COMBAT & OPERATIONAL STRESS CONTROL

Acknowledgement for funding support

- This work is supported in part by VA Medical Merit Review Grant (PI: Huang).

- THANK YOU!

- mxhuang@ucsd.edu